Treatment of lymphangioleiomyomatosis and Camões

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Rogério Rufino[1]

In 1958, Laipply and Sherrick reported the case of a patient with chylous effusion and intrathoracic angiomyomatous hyperplasia, later recognized as the first case report of lymphangioleiomyomatosis (LAM).[1] In the past 57 years, much has been learned about LAM, which is a rare, chronic multisystem disease that predominantly affects women and is characterized by cyst formation (lung destruction), chylous effusion, and extrapulmonary lesions such as angiomyolipomas, lymphatic tumors, and lymphangioleiomyomas.[2] An autosomal dominant disease, LAM is caused by mutations in the *TSC1* or *TSC2* genes; clinical presentations of LAM include cognitive deficit, autism, and convulsions, as well as hamartomas of the brain, heart, skin, kidneys, eyes, lungs, and liver.[2] The disease can be sporadic, resulting from somatic mutations in the *TSC2* gene (mutations that are not passed on to subsequent generations).[2] The pathological features of LAM result from the proliferation of neoplastic cells (LAM cells), which have characteristics of melanocytes and smooth muscle cells.[2] The disease has been considered a low-grade, destructive, metastasizing neoplasm.[3] A diagnosis of LAM is based on the following: thin-walled lung cysts on chest HRCT; history of tuberous sclerosis; family history of LAM; pneumothorax; elevated blood levels of VEGF (≥ 800 pg/mL); lymphangioleiomyomas and angiomyolipomas on abdominal CT or magnetic resonance imaging; chylous effusion; or LAM cells and HMB-45 detection in lung biopsy specimens.[4] The diagnosis of LAM has improved in recent decades, and the therapeutic approach to the disease changed beginning in 2000, when mutations in the *TSC2* gene were first described. Mutations in the *TSC2* gene result in increased protein synthesis and cell growth via stimulation of the mammalian target of rapamycin (mTOR) pathway.[5] Drugs such as sirolimus and everolimus have been evaluated for use in LAM because they have an inhibitory effect on mTOR, specifically on mTOR complex 1.[4] This means that they can reduce or control mutation-induced hyperstimulation of mTOR. An open-label trial published in 2008 showed that the use of sirolimus in the treatment of LAM resulted in a reduction in renal angiomyolipoma volume, which increased again after the drug was discontinued.[5] Currently, mTOR inhibitors are considered effective in treating thoracic manifestations (chylothorax) and extrathoracic manifestations (angiomyolipoma), as well as in stabilizing lung function in patients with LAM.[3] In a case series published in the May-June 2015 issue of the JBP, Freitas et al.[6] reported that sirolimus is beneficial for patients with LAM, especially those with extrapulmonary manifestations. The results are encouraging, showing a reduction in renal angiomyolipoma volume, abdominal mass volume, and retroperitoneal mass volume, as well as resolution of chylothorax. In addition, sirolimus was effective in stabilizing lung function. That was the first study in Brazil to show that sirolimus is a viable treatment option for LAM. However, according to the authors, certain issues, such as the optimal dose, duration of treatment, and long-term safety, have yet to be clarified.[6] Nevertheless, there have been promising advances in the management of LAM. In fact, there are new treatment options for other interstitial diseases. Pirfenidone and nintedanib, the first drugs to be specifically designed for the treatment of idiopathic pulmonary fibrosis, have recently been approved for use in the USA, representing an important therapeutic advance.[7,8] New drugs are currently being evaluated for use in patients with refractory sarcoidosis and in those with refractory systemic sclerosis.[9,10] In addition, lung transplantation is now well established as a treatment option for interstitial diseases, as demonstrated by Rubin et al.[11] in a study published in the current issue of the JBP; the authors reported a mean increase in FVC of 620 mL from baseline to the first year of follow-up in patients with idiopathic pulmonary fibrosis undergoing single lung transplantation; however, 30% of the patients died before the first year of follow-up.

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There are new therapeutic directions in the management of interstitial lung diseases. Therefore, I refer to *Canto* VI of *Os Lusíadas*:

Outras palavras tais lhe respondia
O Capitão, e logo, as velas dando,
Para as terras da Aurora se partia,
Que tanto tempo há já que vai buscando.
No piloto que leva não havia
Falsidade, mas antes vai mostrando
A navegação certa; e assim caminha
Já mais seguro do que dantes vinha.

- Luís Vaz de Camões (1524 – 1579)
in Os Lusíadas,[2] Canto VI

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2 An epic poem, written in Homeric style, regarded by many as the national epic of Portugal. In this passage, the captain of the Portuguese fleet reaffirms the correctness of his course and sails onward, more confident than ever, toward his destination (the port of Kozhikode, in India).

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